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Psilocybin-Assisted Psychotherapy: Treating Depression and Anxiety with Mushrooms

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ABSTRACT

Depression and anxiety are debilitating mental health conditions that affect a large portion of the United States. Current pharmacological treatments for these disorders require daily administration, are associated with a number of side effects, and can be ineffective for some. Emerging evidence in novel treatment options may necessitate a shift toward how we treat these psychiatric disorders.

Studies involving the psychedelic serotonin agonist, psilocybin, are currently experiencing a resurgence as an alternative for patients who are unresponsive to traditional treatments. Clinical trials using psilocybin in combination with psychotherapy have demonstrated sustained reductions in depression and/or anxiety symptoms. When used in medical settings, it has shown to be safe, with few side effects and no risk of dependence. However, this psychedelic compound faces many stigmas and these results have yet to be compared to current treatments or in larger populations. Psilocybin represents a promising field of research that warrants more robust studies in order to gain societal approval and establish a role in treating common psychiatric diagnoses.

INTRODUCTION

Depression is one of the leading causes of disability worldwide.[1] According to the National Institutes of Health (NIH) in 2017, an estimated 17.3 million adults in the United States had at least one major depressive episode. This number represented over 7% of all U.S. adults. The total economic burden of major depressive disorder is estimated to be more than $210 billion each year in the U.S.[2] Therapy and antidepressants are some of the most commonly used treatments for depression, but approximately 20% of patients do not respond to any type of

intervention.[3,4] Conventional antidepressants such as SSRIs and SNRIs come with undesired side effects, delayed therapeutic onset, or in some cases a complete lack of response.[4,5] In search of more effective treatment options, scientists are taking a refreshed look at psychedelic compounds, such as lysergic acid diethylamide (LSD), ayahuasca, and psilocybin, to treat the growing mental health crisis plaguing our society.

Psilocybin is showing promising results in treating a number of psychiatric disorders when combined with psychotherapy. While only small studies have been conducted, psilocybin has safely exhibited rapid and sustained antidepressant and anxiolytic effects after the administration of just one or two doses.[6,7] These results could imply a reduced need for daily medications with an alleviation of symptoms for weeks or even months. It is important for today's medical providers to be informed of the progressing studies involving psilocybin, as they have the potential to treat patients suffering from depression who have found mainstream therapies unsuccessful.

This article examines the efficacy of psilocybin and its potential use in treating some of the most common mental health conditions seen by primary care and behavioral medicine providers. Other psychedelics are being investigated to treat various psychiatric diseases, however, this article will only focus on psilocybin use in patients suffering from depression and/or anxiety. The purpose of this article is not to promote the recreational use of psychedelics outside of a clinical setting with trained specialists.

BACKGROUND

For thousands of years, psilocybin has been used in religious, medicinal, and ceremonial practices around the world.[8] It was first isolated and synthesized by the Swiss chemist Albert

Hofmann in 1958.[9] At the time of its introduction to Western society, psychiatry lacked effective medical therapies to treat mood, anxiety, and addictive disorders.[9] Researchers quickly discovered psilocybin had therapeutic potential for treating these conditions and a low risk of toxicity.[9] Hundreds of papers were published displaying the efficacy of psychedelics at treating non-psychotic mood disorder patients who failed to make progress with medication or therapy.[9] However, widespread recreational misuse of psychedelics led to their association with the counterculture in the 1960s. In 1967, the U.S. declared psychedelics, including psilocybin, Schedule I drugs.[9] Compounds in this classification are deemed to have no accepted medical use and a high potential for harm and chemical dependence.

Over the last decade, there has been a resurgence of studies using psilocybin in combination with psychotherapy to treat depression, anxiety, obsessive compulsive disorder (OCD), addiction, cluster headaches, and most recently anorexia nervosa.

HOW IT WORKS

Psilocybin, commonly known as "magic mushrooms", is a naturally occurring compound found in a variety of mushroom species.[4,10] Following ingestion, psilocybin is broken down to its psychoactive metabolite, psilocin (4-hydroxy-N, N-dimethyltryptamine).[11] Psilocin acts as an agonist to 5-HT_{2A} serotonin receptors in the brain.[8,11,12] While it is not completely understood, scientists believe that this interaction is what attributes psilocybin to hallucinogenic and euphoric effects. By increasing serotonergic signals, psilocybin reduces depression and anxiety, while increasing positive mood state.[12] Functional magnetic resonance imaging (fMRI) evidence suggests that psilocybin produces these symptoms by affecting the amygdala and an area of the brain called the default mode network (DMN).[12,13] This neuronal network is largely responsible

for the ego, sense of self, and perceptions of the outside world. Hyperactivity of the DMN has been linked to negative self-referential and ruminating thoughts commonly associated with depression and anxiety.[4,8,10] By decreasing DMN activity, individuals experience mental flexibility leading to positive changes in attitude, mood, perspective, values, and behavior.[4,12,14] This allows patients to accept their emotions and process them. According to studies, these effects are rapid and can last long after their session is over, even in conditions notorious for resistance to treatment.[7,10,13,14]

In clinical trials, psilocybin is administered to participants in a controlled environment. Preparatory sessions are performed by trained psychiatrists to discuss patient's personal history (including thoughts and origins of depression or anxiety), psychological effects of psilocybin, and a simulation of the dosing session.[13] The psilocybin is delivered in a clear or opaque capsule and consumed orally. During administration, patients are placed in a supine or relaxed position, given eyeshades and headphones (to reduce any outside stimuli), and are psychologically supported whenever needed. Patients are supervised at all times and are assessed periodically throughout the four to six hour session. After each dosing session, patients attend further visits to discuss the experience and integration into their life.

FINDINGS

Over the past decade, studies conducted at research institutions like Johns Hopkins University School of Medicine, New York University, and Imperial College of London have shown measurable benefits in early trials. In all studies to date, administration resulted in statistically significant reductions in symptoms and clinical improvements in anxiety or depression.[4] The largest of the completed clinical trials have been on patients who experience

psychological distress associated with a life-threatening illness. Two double-blind, randomized, crossover trials investigated the effects of psilocybin on symptoms of depression and anxiety in patients with terminal cancer.[7,14] In 2016, Griffiths et. al studied the effects of psilocybin in cancer patients (n=51) with life-threatening diagnoses and symptoms of depression and/or anxiety in a randomized, double-blind, cross-over trial with very low dose versus high dose psilocybin.[14] Two counterbalanced dosing sessions were held five weeks apart and a six month follow-up was conducted. The study found that the treatment produced large decreases in depressed mood and death anxiety, along with increases in optimism and quality of life.[14] Six months after their dosing sessions, 78% of the patients with depression and 83% with anxiety showed persistent symptom remission. Furthermore, 80% of all participants stated that their experience increased their well-being or life satisfaction.[14]

A recent open-label pilot study examined psilocybin administration in individuals (n=12) with treatment-resistant depression. All participants were diagnosed with moderate to severe depression, lasting on average 17.8 years, and had no improvement despite two or more courses of antidepressant treatments.[13] These patients received an initial safety session of low dose psilocybin (10 mg), then the second session of a higher dose (25mg) was performed seven days later.[4,13] One week after the administration, 67% of the patients showed a response to treatment and reduction in their depressive symptoms. Three months after, 58% maintained response, and 42% met criteria for complete remission.[13] These results have implications for patients who have failed to respond to all other forms of therapy and medication currently available and warrant further study.

SAFETY

Clinical studies have shown psilocybin therapy to be well tolerated, safe, and with minimal side effects.[12-15] The most common adverse effects include transient anxiety, nausea, vomiting, and mild increases in blood pressure and heart rate.[6,9] Shortly after medication onset, patients can experience emotional and perceptual changes that can be varied and intense. Individuals can often become frightened, disoriented, or more anxious during the treatment. Fortunately, none of the conducted studies in the last 25 years produced prolonged psychosis, persisting hallucination, or required any medical intervention.[4,6,9] In terms of dependence, there has been no reported risk.[4] Current phase two trials being performed by COMPASS Pathways are exploring the safety and efficacy of psilocybin in 200 participants and should conclude by the end of 2020 (ClinicalTrials.gov, number NCT03775200). The potential for abuse, although very low, is due to repeated daily intake causing downregulation of serotonin receptors and rapid tolerance.[4] In fact, studies of alcohol and smoking cessation indicate psilocybin may have anti-addictive properties.[16,17] These findings suggest that it can be safely administered to patients in a controlled setting.

CONCLUSION

Given the promising results of small clinical trials, psilocybin may have a role in the treatment of depression and/or anxiety, with some evidence for a role in treatment-resistant major depressive disorder. Nevertheless, psilocybin remains a Schedule I drug and much of how it benefits patients remains unknown. As of now, clinical trials have small sample sizes and are short in duration. Before it is legalized and used in practice, we must be certain of the long-term effects in larger populations. Additionally, there is a need to conduct contrasting antidepressant

studies, such as the ongoing randomized trial comparing psilocybin to the SSRI escitalopram (ClinicalTrials.gov, number NCT03429075).

As a stigmatized substance, there are regulations that stand in the way of gaining imperative data, however, we must pursue research in this field to find alternative methods of alleviating debilitating human conditions. Providers in psychiatry and primary care settings are at the forefront of helping patients with their mental health ailments. Regardless of the chosen remedy, we suggest that medical providers remain vigilant in novel treatment options and that we expand our 'best practice' in treating common mental health conditions. Ultimately, these mushrooms may not be for everyone, but for some, they could be magic.

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